Br. J. clin. Pharmac. (1985), **20**, 339–344

Studies on the pharmacological control of gastric emptying in man

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1 Three compounds with differing pharmacological properties have been studied with respect to their effects on gastric emptying, BP, pulse rate and sedation in comparison with placebo in three groups of normal male volunteers.

2 BRL 20627 (10 mg i.v.), a benzamide without dopamine antagonist activity, increased gastric emptying rate ($t_{0.5}$ BRL 20627 8.3 ± 0.87 min, placebo 13.8 ± 2.29 min, $P <$ 0.005).

3 Zetidoline (20 mg orally), a dopamine D_2-receptor antagonist had no significant effect on gastric emptying parameters.

4 BK 34/530 (50 and 100 mg orally) a compound with mixed dopamine agonist and α-adrenoceptor antagonist activity, impaired gastric adaptive relaxation as measured by the volume 5 min after the drink and at the higher dose delayed gastric emptying (placebo—5 min volume 256 ± 44.3 ml, $t_{0.5}$ 15.3 ± 1.32 min: 50 mg BK 34/530—5 min volume 247 ± 38 ml, $t_{0.5}$ 14.2 ± 1.94 min: 100 mg BK 34/530—5 min volume 228 ± 43.7 ml, $t_{0.5}$ 21.1 ± 3.82 min).

5 All three drugs resulted in small but significant falls in blood pressure, and in the case of BK 34/530 the 100 mg dose caused significant tachycardia.

6 These studies suggest that dopamine antagonist activity is not a prerequisite for 'gastrokinetic' effects in man, and that there is no inhibitory dopaminergic tone on gastric emptying in normal subjects.

Keywords gastric emptying dopamine receptors dopamine antagonists

Introduction

Although the neurotransmitters involved in the control of gastric emptying in man are uncertain, one transmitter that has been suggested as being involved is dopamine (Valenzuela, 1976). Dopamine delays gastric emptying in animals (Van Neuten & Janssen, 1978) and man (Bateman, 1983) and the dopamine antagonist metoclopramide has been shown to increase gastric emptying rate (Kreel *et al.*, 1972).

There is, however, some controversy regarding the role of dopamine in the control of gastric emptying (Valenzuela & Dooley, 1984), since the effects of dopamine agonists could be central, and metoclopramide has effects on acetylcholine release which may account for its actions on the gut (Fosbraey *et al.*, 1980; Hay, 1977; Kilbinger *et al.*, 1982). The studies described in this paper were carried out to investigate the effects of three compounds with different pharmacological effects on gastric emptying in man.

BRL 20627 (2 α, 6 β, 9a α-(±) -4, -amino, -5, -chloro, -2, -hydroxy, -*N*- (octahydro-6-methyl-2H-quinolizin-2yl)benzamide), has the same effects as metoclopramide on *in vitro* gut preparations (McClelland & Sanger, 1983) but is devoid of dopamine receptor antagonist activity as assessed by effects on prolactin release (McClelland *et al.*, 1983).

Zetidoline (±- 308-17:1-(3-chlorophenyl)-3-(-2-(3,3 dimethyl-1-azitidinyl ethyl)imidazoline-2-one hydrochloride) is a selective D_2-receptor antagonist antipsychotic (Barbieri *et al.*, 1984).

It also has a weak effect on presynaptic cholinergic receptors in the gut, the site at which metoclopramide also acts (Fosbraey *et al.*, 1980). BK 34/530 (5,6,7,8,-tetra hydro-6-[4-2-methylphenyl)-1-piperazinyl]naphthalen-2-ol) is a compound with mixed dopamine agonist and α-adrenoceptor antagonist activity (Walden *et al.*, 1985).

Methods

Three groups of healthy male volunteers participated in these studies which were approved by the University of Newcastle upon Tyne Ethics Committee.

On each study day volunteers attended the clinical laboratory after an overnight (12 h) fast having refrained from ethanol for 36 h. Treatments were administered in random order at least 1 week apart, and subjects were seated throughout the study period. The designs of the studies with zetidoline and BK 34/530 were similar since both were only available as an oral preparation. On each study day matched active or placebo tablets were administered with 100 ml of water after basal physiological readings had been obtained. Zetidoline (20 mg) and BK 34/530 (in doses of 50 mg and 100 mg) were compared to placebo in separate groups of eight and seven subjects respectively. In the case of BRL 20627 active drug (20 mg), or matched placebo, was given by intravenous injection and compared in eight subjects.

Blood pressure was measured in duplicate using a random-zero sphygmomanometer and pulse rate recorded by ECG telemetry. For the oral studies with BK 34/530 and zetidoline readings were taken before administration of drug or placebo and at 15 min intervals for 2 h. In the case of BRL 20627 pulse and blood pressure were measured before drug or placebo administration and at 10, 25, 40 and 70 min afterwards. Sedation was measured using 100 mm visual analogue scales with limits of 'wide awake' and 'nearly asleep'.

Gastric emptying was measured as previously described (Bateman & Whittingham, 1982) using real-time ultrasound. A drink of 500 ml orange cordial at 37° C was consumed 1 h after oral treatment, or in the case of intravenous drugs 10 min after the injection. Gastric volume was measured at regular intervals from 5 min after the drink.

Spontaneous reports of adverse effects were noted and subjects were observed for symptoms of motor restlessness (akathisia).

Data analysis

Gastric emptying of the liquid meal used in these experiments is characterised by an initial rapid phase of emptying, which occurs within the first minutes of drinking and reflects the phase of adaptive relaxation, followed by a slower mono-exponential decline (Bateman, 1982). The initial phase can be assessed from the 5 min volume measurement, or by back extrapolating the subsequent mono-exponential decline to zero time (intercept volume). The mono-exponential decline is expressed as a half-life.

Mean blood pressure was measured as diastolic blood pressure plus one third of the pulse pressure. Sedation was assessed on the visual analogue scale, the limits of which were 'wide awake' and 'nearly asleep' by measuring the distance in mm from 'wide awake'.

Results are expressed as mean ± s.e. mean. Statistical analysis of gastric emptying and cardiovascular data was paired *t*-test and analysis of variance. Sedation scores were compared by the Wilcoxon signed rank test.

Results

Gastric emptying

The three drugs studied all had different effects on gastric emptying. BRL 20627 significantly decreased the half-life of gastric emptying (Figure 1, Table 1) (BRL 8.3 ± 0.87 min; placebo 13.8 ± 2.29 min, $P < 0.005$). There was no significant difference in the intercept volume (BRL 292 ± 61 ml, placebo 258 ± 29.2 ml) but the 5 min volume was significantly reduced by active drug (BRL 174 ± 29.4 ml, placebo 222 ± 26.8 ml, $P < 0.02$). Thus BRL 20627 increased the rate of emptying of liquid in the mono-exponential phase.

Zetidoline had no significant effect on the parameters of gastric emptying measured (half-life: zetidoline 17.2 ± 4.13 min, placebo 14.7 ± 2.43 min: 5 min volume: zetidoline 167 ± 30.7 ml, placebo 181 ± 38.8 ml, intercept volume: zetidoline 216 ± 35.9 ml, placebo 214 ± 50.2 ml).

BK 34/530 reduced the 5 min volume (placebo 256 ± 44.3 ml, 50 mg BK 34/530 214 ± 39.3 ml, 100 mg BK 34/530 203 ± 42.3 ml) and this difference was statistically significant for the 50 mg dose ($P < 0.01$). Similar trends were observed for the intercept volume but these were not statistically significant (placebo 300 ± 50.9 ml, BK 34/530 50 mg 247 ± 38 ml, BK 34/530 100 mg 228 ± 43.7 ml). The effect on half-life of empty-

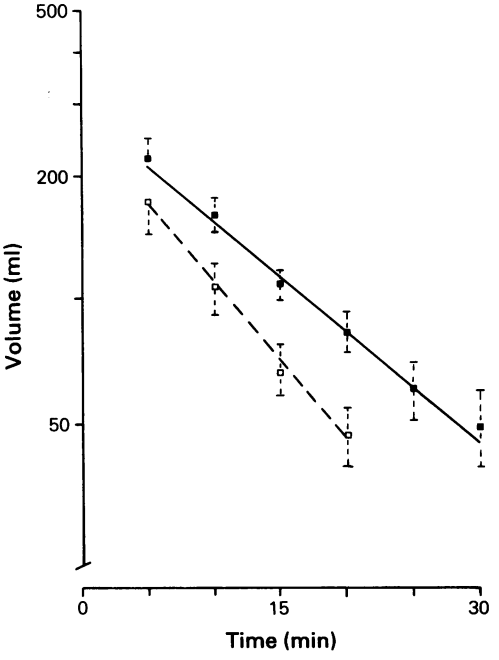

Figure 1 Effect of BRL 20627 (□) and placebo (■) on gastric emptying. The effect of BRL 20627 was significantly different from placebo ($P < 0.005$).

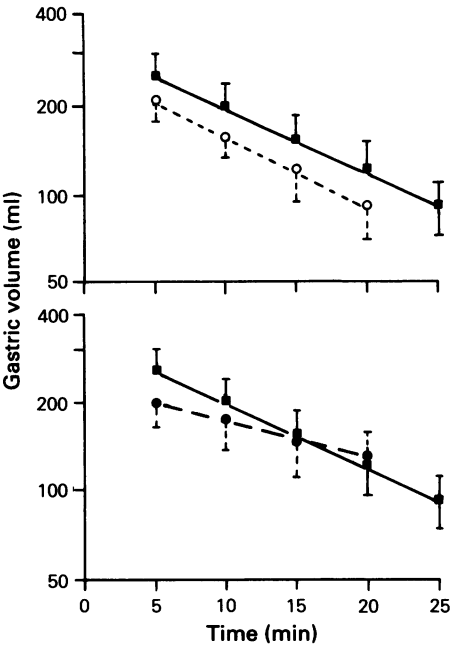

Figure 2 Gastric emptying of liquid following placebo (■), BK 34/530 50 mg (○)—upper panel and BK 34/530 100 mg (●) lower panel—see text for details.

ing was dose dependent (placebo 15.3 ± 1.32 min, BK 34/530 50 mg 14.2 ± 1.94 min, BK 34/530 100 mg 21.1 ± 3.82 min). The difference between the 50 mg and 100 mg dose on the half-life was significant at the 1% level. In summary BK 34/530 at a dose of 50 mg significantly impaired gastric adaptive response while at the higher dose this effect was accompanied by a delay in the mono-exponential phase of emptying (Figure 2).

Cardiovascular effects

BRL 20627 produced a significant fall in mean blood pressure (Anova $P < 0.01$) over the period of the experiment (Figure 3), the maximum fall in blood pressure being at 40 min (77 mm Hg compared to placebo). Pulse rate was not significantly changed by this drug. Zetidoline also resulted in a fall in mean blood pressure ($P < 0.05$), the maximum effect being 90 min after

Table 1 Parameters of liquid gastric emptying (mean ± s.e. mean) in three groups of normal male subjects following treatment with placebo or BRL 20627 (20 mg i.v.), zetidoline (20 mg orally) and BK 34/530 (50 mg and 100 mg orally).

		Intercept volume (ml)	*5 min volume (ml)*	*Half-life (min)*
BRL 20627	Placebo	292 ± 61	222 ± 26.8	13.8 ± 2.29
($n = 8$)	Active 20 mg i.v.	258 ± 29.2	174 ± 29.4[a]	8.3 ± 0.87[b]
Zetidoline	Placebo	216 ± 35.9	181 ± 38.8	14.7 ± 2.43
($n = 8$)	Active 20 mg oral	214 ± 50.2	167 ± 30.7	17.2 ± 4.13
BK 34/530	Placebo	300 ± 50.9	256 ± 44.3	15.3 ± 1.32
($n = 7$)	Active 50 mg oral	247 ± 38.0	214 ± 39.3[c]	14.2 ± 1.94
	Active 100 mg oral	228 ± 43.7	203 ± 42.3	21.1 ± 3.82[d]

[a] Significantly different from placebo $P < 0.02$
[b] Significantly different from placebo $P < 0.005$
[c] Significantly different from placebo $P < 0.01$
[d] Significantly different from 50 mg dose of BK 34/530 $P < 0.01$

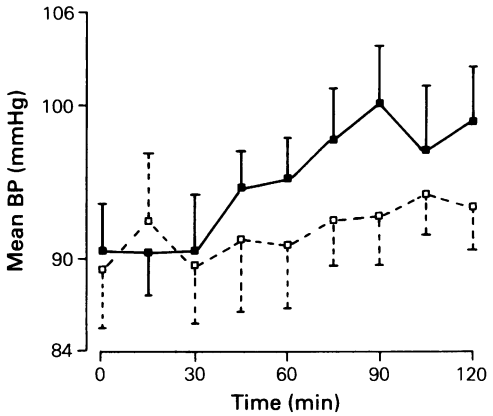

Figure 3 Effect of zetidoline (□) and placebo (■) on mean blood pressure. The effect of zetidoline was significantly different from placebo ($P < 0.05$).

the oral dose (Figure 4). Pulse rate was not significantly changed.

BK 34/530 at a dose of 50 mg resulted in a fall in mean blood pressure, the mean difference being 6 mm Hg at 60 min ($P < 0.02$). At this dose there was no significant change in pulse rate. Following 100 mg BK 34/530 blood pressure was not significantly altered, but pulse rate rose significantly ($P < 0.02$) compared with placebo from 60 min with a maximal increase of 12 beats min^{-1} at 75 min after dosing (Figure 5).

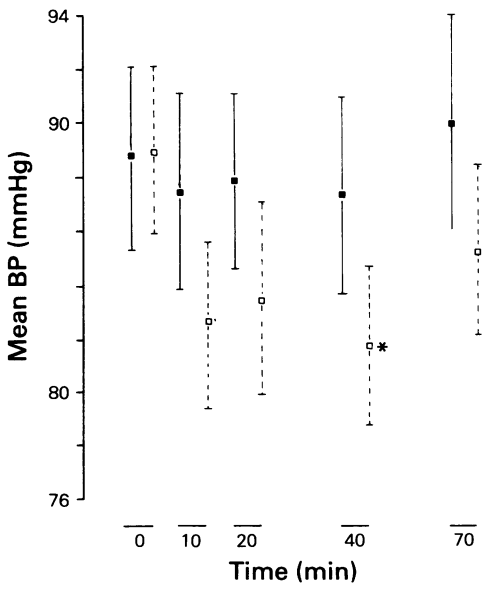

Figure 4 Effect of BRL 20627 (□) and placebo (■) on mean blood pressure. The effect of BRL 20627 was significantly different from placebo ($P < 0.02$).

CNS effects

BRL 20627 treatment resulted in no significant change in visual analogue scores of sedation. One volunteer complained of restlessness after active drug.

Zetidoline produced significant changes in visual analogue sedation with a maximal effect at 90 min (Figure 6). In addition, six volunteers experienced akathisia with active drug.

BRL 20627 at 100 mg resulted in sedation in five of the seven volunteers. No other adverse effects were noted.

Discussion

In these experiments the effects of three different drugs have been studied on gastric emptying, blood pressure, pulse rate and sedation.

The investigation of the effects of drugs on gastric emptying *in vivo* is complicated by inter and intra individual differences in response. The ultrasound technique of gastric emptying measurement used has a mean coefficient of variation of 12% within subjects, but a much larger variation is observed between subjects. In the experiments presented different groups of male volunteers were studied, and so there is a degree of variation in the control observations. Furthermore the studies using oral treatments are clearly not directly comparable to those in which an intravenous preparation was used (BRL 20627). The amount of liquid consumed with the oral tablets was small, however, and had left the stomach before the test meal. An effect on the emptying of the test meal cannot be excluded, but was controlled for on the placebo day.

All three drugs had different effects on gastric emptying. Zetidoline, a dopamine antagonist, had no significant effect on gastric emptying, despite evidence of pharmacological activity on the central nervous and cardiovascular systems. Other workers have also demonstrated a highly significant rise in prolactin with this dose and route of administration. In view of the lack of effect of zetidoline it seems unlikely that dopamine D_2-receptors exert tonic inhibitory control on the stomach.

The effect of BRL 20627 in increasing gastric emptying were predicted from animal studies. This compound is of interest, however, in that it does not elevate serum prolactin in experimental animals or man (McClelland *et al.*, 1983). It therefore would appear devoid of significant dopamine D_2-receptor antagonist activity. In the current studies the effects of BRL 20627 were similar to those previously observed with meto-

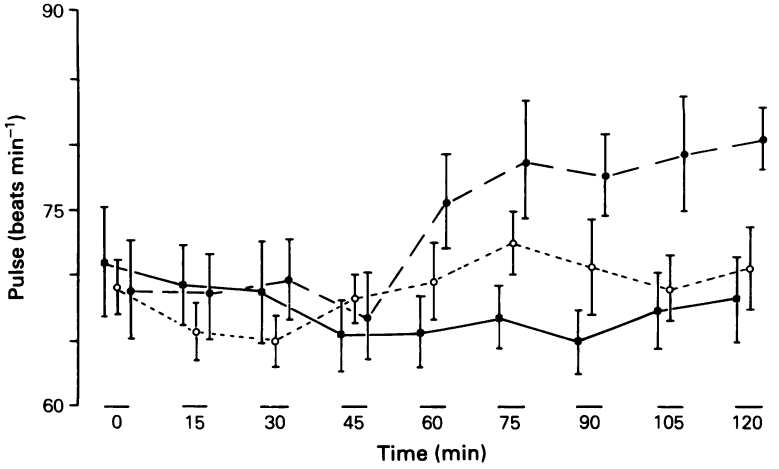

Figure 5 Effect of placebo (■) BK 34/530 50 mg (□) and 100 mg (□) on pulse rate. The effect of BK 34/530 100 mg were significantly different to placebo ($P < 0.02$).

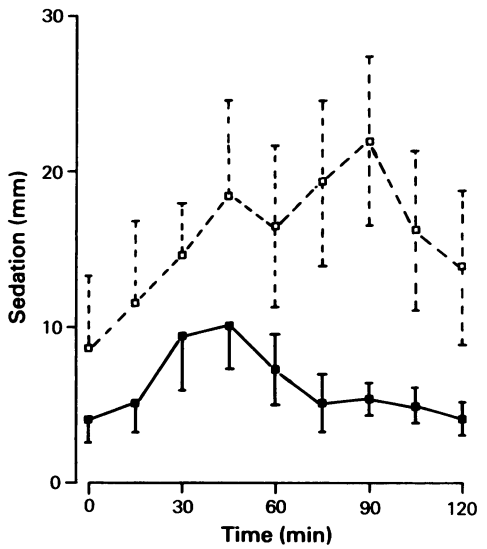

Figure 6 Effect of zetidoline (□) and placebo (■) on visual analogue sedation. The effect of zetidoline was significantly greater than placebo ($P < 0.02$).

clopramide (Bateman & Whittingham, 1982). Since both BRL 20627 and metoclopramide have an effect on acetylcholine release in the gut (McClelland & Sanger, 1983), but differ in their effects on dopamine receptors (McClelland *et al.*, 1983), these data support the hypothesis that dopamine antagonism is not the primary mechanism of action of metoclopramide on the stomach. This also suggests that dopamine receptor antagonism is not a prerequisite for a gastrokinetic action of drugs, a finding in keeping with the observed lack of effect of zetidoline.

The effects of BK 34/530 on the emptying of liquid from the stomach in these experiments varied with dose. A 50 mg dose produced no change in half-life of emptying but significantly reduced the 5 min volume measurement. The 100 mg dose of the drug also delayed the mono-exponential phase of emptying when compared to the 50 mg dose. *In vivo* BK 34/530 displays both α-adrenoceptor antagonist and dopamine agonist activity (Walden *et al.*, 1985). In previous studies using the same methodology for measuring gastric emptying domperidone had similar effects to 50 mg BK 34/530 (Bateman *et al.*, 1982). Since the only pharmacological property these drugs appear to share is α-adrenoceptor antagonism (Costall *et al.*, 1981; Ennis & Cox, 1980) it is tempting to suggest this is the pharmacological action responsible for these observations. Although there is data on the effects of β-adrenoceptor agonists and antagonists (Rees *et al.*, 1980) on gastric emptying in man the effects of α-adrenoceptor blockers do not appear to have been investigated. At the higher dose BK 34/530 significantly slowed the mono-exponential phase of gastric emptying and this effect, being similar to that seen when dopamine is infused to normals (Bateman, 1983), presumably reflects dopamine agonist activity.

The cardiovascular effects of all these drugs were similar, with a small but significant fall in mean blood pressure. At the higher dose BK 34/530 produced a significant tachycardia, which would be compatible with a compensatory response to vasodilation. The cardiovascular

effects of BK 34/530 differ from those observed with dopamine (Bateman, 1983; Gundert-Remy *et al.*, 1984).

Central nervous system effects studied were on sedation. Zetidoline, as expected, produced the most sedation, and also akathisia. BRL 20627 produced no sedation and BK 34/530 sedation only at the higher dose studied.

In conclusion these studies highlight the complexities of the pharmacology of gastric emptying in man. They do not lend support to the hypothesis that dopamine receptors are closely involved in the inhibitory control of gastric emptying in normal subjects but suggest α-adrenoceptors may have a role in the human stomach. Some workers report an effect of drugs such as metoclopramide only in subjects with an initial delay in gastric emptying (Metzger *et al.*, 1976), and it may be that in such subjects there is a degree of tonic dopamine inhibition. The data obtained in the current studies however, suggest that other pharmacological properties may well be responsible for the gastrokinetic effects of drugs on the human stomach. Actions on presynaptic cholinergic (Fosbraey *et al.*, 1980), tryptaminergic (Kilbinger *et al.*, 1982), or α-adrenoceptors (Costall *et al.*, 1981) appear potential candidates as sites for such effects.

These studies were supported in part by Beecham Pharmaceuticals, Sandoz and Merrell Dow. The ultrasound equipment used in this study was purchased with a grant from the Wellcome Trust.

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(Received 4 March 1985, accepted 15 June 1985)